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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Nigel L. Webb, et al.
Serial No.	:	09/265,307
Confirmation No.		4390
Filing Date	:	March 9, 1999
For	:	FATTY ACID-ANTICANCER CONJUGATES AND USES THEREOF
Examiner	:	B. Trinh
Art Group	:	1625

CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8(a)

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Edward R. Gates

Mail Stop: Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION

1. I am an associate professor in the Department of Pharmaceutical Sciences, University at Buffalo, State University of New York. I have studied the pharmacokinetics of anti-cancer therapies for more than 10 years. A copy of my CV is attached.

2. I have reviewed the above-identified patent application, the pending claims, the Office Action dated 1/13/04, and the cited prior art references: Yoshida et al., Kataoka et al., and Rentsch et al.

3. As indicated in the Office Action, several pending claims (1, 5, 7, 12, 17, 21, 23, 33, 119-201, 123-126, 128-131, 134-136, 139-142, 188-201) have been rejected based on obviousness. The Office Action argues obviousness based on the teachings of Yoshida et al., Kataoka et al., and Rentsch et al., which were cited as demonstrating that fatty-acid anticancer conjugates allow "increases of the dosage of the conjugated drug without harming the body." In my opinion, this conclusion is very flawed.

4. The Yoshida et al. report investigated the administration of an acyl derivative of arabinofuranosylcytosine (BH-AC), which was administered at doses ranging from 500mg/m^2 to

1300mg/m^2, in 10 patients diagnosed with non-Hodgkin's lymphoma. This was a very small study, where dose levels (500, 700, 900, and 1300 mg/m^2) were administered to groups of three patients on a 5-consecutive day schedule. The Yoshida et al. report did not investigate toxicity resulting from the administration of the parent compound (arabinofuranosylcytosine, Ara-C). As such, there is no comparison of the maximum tolerated dose (MTD) of BH-AC and Ara-C in this treatment group.

5. The treatment group was heavily pre-treated, as Yoshida et al. state that the patients were "tolerant to conventional multiple medication treatment, and had experienced BH-AC treatment...in the past." This treatment group therefore would likely have a different MTD than for the normal patient population, and the MTD for this group was not measured or discussed. In fact, it is possible that the MTD of Ara-C and BH-AC in such patients are **dramatically** different than those in the normal patient population. Consequently, it is not appropriate to compare of the doses of BH-AC applied in the Yoshida et al. study (i.e., 500 – 1300 mg/m^2) to the maximum tolerated dose of Ara-C found in other groups of patients (i.e., that were not tolerant to multiple medication treatment, including past treatment with BH-AC).

6. No statistical analyses were performed by Yoshida et al. to compare the MTD of BH-AC to the MTD of Ara-C. Differences observed within treatment groups (e.g., with regard to the maximum tolerated dose of drug) may be a chance observation resulting from the use of small samples of patients and/or high inter-patient variability in the metric of interest (e.g., MTD). Within the scientific literature, differences are typically deemed to be "significant" only when statistical analyses demonstrate that there is less than a 5% probability ($p < 0.05$) that the observed difference is a chance observation.

7. Based on the facts detailed in paragraphs 4, 5 and 6 above, in my opinion, it is not possible to conclude from reading Yoshida et al. that fatty acid drug conjugates of Ara-C may be safely administered at doses exceeding the Ara-C MTD.

8. The Katoaka et al. and Rentsch et al. references do not investigate the development of toxicity following the administration of Ara-C and/or following administration of fatty acid conjugates of Ara-C. Consequently, the teachings of Katoaka et al. and Rentsch et al. do not support the

conclusion in the Office Action that prior art demonstrates that fatty-acid anticancer conjugates allow "increases of the dosage of the conjugated drug without harming the body."

9. The Office Action cites the prior art as teaching that fatty acid conjugation "endows Ara-C with hydrophobicity thus enables BH-AC to be released slowly in the body" and that "the conjugated drug...is released slowly to the body, thus a higher dose can be used and tolerated compared to the parent drug." Through these statements, the Office Action argues that it is obvious that fatty acid conjugation will endow slow release of the drug in the body, prolonging the time-course of circulation of the drug in the body, and allowing increases in the MTD. In my opinion, this argument is also very flawed.

10. Examples exist in the literature to demonstrate that slow release of anti-cancer drugs, where the time-course of drug circulation is prolonged, can actually decrease MTD.

11. To illustrate the degree of variation, in recent work conducted in my laboratory (Lobo ED and Balthasar JP, Pharmacokinetic-pharmacodynamic modeling of methotrexate-induced toxicity in mice, Journal of Pharmaceutical Sciences, 92: 1654-1664, 2003), we investigated the toxicity induced by methotrexate following intra-peritoneal administration in mice. The MTD of methotrexate was highly dependent on the time-course of release of the drug. For example, following administration of methotrexate by rapid ("bolus") injection, we found that MTD was 760 mg/kg. Following slow release of the dose from an osmotic pump over 72 hours, we found that MTD was dramatically reduced to 3.8 mg/kg. Likewise, following slow release of methotrexate from an osmotic pump over 168 hours, MTD was 6.7 mg/kg, still dramatically reduced versus the MTD for a bolus (although slightly increased versus a 72 hour schedule). Statistical analyses demonstrated that for a given dose of methotrexate, the different modes of methotrexate administration led to statistically significant differences in methotrexate-induced toxicity.

12. Additional literature reports demonstrate that prolongation of the release of anticancer drugs may decrease MTD. For example, in a review of phase I clinical studies with topotecan, Rowinsky and Verweij cited data showing that the MTD of topotecan is highly dependent on the mode of topotecan administration, ranging from 22.5 mg/m^2/d when released into the body over

30 min, to 1 mg/m^2/d when released into the body over 72 h (Rowinsky EK and Verweij J, Review of phase I clinical studies with topotecan, Seminars in Oncology, 24: S20-3-S20-10, 1997).

13. In summary, the literature demonstrates that there is no single relationship between the time-course of drug release and MTD. In my opinion, the literature shows that such relationships have been unpredictable for each individual drug. As such, despite the teachings of Yoshida et al., Kataoka et al., and Rentsch et al., it would not have been obvious, as of the 1999 filing date of the above application, that fatty-acid drug conjugates would permit higher doses than for the parent compounds. The prior art does not suggest the conclusion by the examiner that "a higher dose can be used and tolerated [for a fatty acid drug conjugate] compared to the parent drug."

14. It also was well known at the time of the filing of the above patent application that the Maximum Tolerated Dose (MTD) of a specific drug depends on the mode of administration of that drug. The literature clearly shows that the MTD of a specific drug depends on the mode of administration of that drug.

15. For the reasons outlined above, I disagree with the opinions stated in the Office Action, including the conclusion that "...the claimed invention would be deemed obvious over the teachings of the prior art since the addition of the fatty acid to the cancer drug (Ara-C) would enable the increase of the dosage of the conjugated drug without harming the body."

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above application and any patent or application related thereto.

Joseph P. Balthasar, Ph.D.

7/6/2004
Date